PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 27.14.81642/002	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/004341	International filing date *(day/month/year)* 13.10.2004	Priority date *(day/month/year)* 13.10.2003
International Patent Classification (IPC) or national classification and IPC A61K38/29, A61P3/10		
Applicant CREATIVE PEPTIDES SWEENEN AB et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.07.2005	12.01.2006
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ganschow, S Telephone No. +49 89 2399-7807

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004341

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-21	as originally filed

Sequence listings part of the description, Pages

22, 23	as originally filed
24-31	received on 21.02.2005 with letter of 17.02.2005

Claims, Numbers

1-9	received on 11.07.2005 with letter of 07.07.2005

Drawings, Sheets

1/3-3/3	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004341

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3-9

because:

☒ the said international application, or the said claims Nos. 3-9 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004341

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,3
	No:	Claims	2,4-9
Inventive step (IS)	Yes:	Claims	1,3
	No:	Claims	2,4-9
Industrial applicability (IA)	Yes:	Claims	1,2
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 3 (and the hereto dependent claims 4-9) relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Documents

1.1. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 02/38129 A2 (CREATIVE PEPTIDES SWEDEN AB; GARDNER, REBECCA; MOHR, DETLEF; SEIFFERT,) 16 May 2002 (2002-05-16)

D2: WO 02/22211 A2 (CREATIVE PEPTIDES SWEDEN AB; GARDNER, REBECCA; WAHREN, JOHN; JOHANSSON) 21 March 2002 (2002-03-21)

D3: US 2002/077317 A1 (DAS UNDURTI NARASIMHA) 20 June 2002 (2002-06-20)

D4: US 2003/180332 A1 (RIMPLER STEPHAN ET AL) 25 September 2003 (2003-09-25)

D5: Sima A A F; Zhang W; Sugimoto K; Henry D; Li Z; Wahren J; Grunberger G: "C-peptide prevents and improves chronic Type I diabetic polyneuropathy in the BB/Wor rat"; Diabetologia 2001; Vol. 44 (7), 889-897

2. Novelty

2.1. D2 teaches a pharmaceutical composition comprising C-peptide for administration to a patient 1 to 6 times during the course of a day (page 9, line 19-24). D2 explicitly states that **sustained release formulations are preferably given at longer intervals**, e.g. 1 to 2 times a month or every three month.

Consequently, the composition of present claim 2 cannot be considered novel in view of D2.

2.2. Newly cited document D5 discloses a pharmaceutical composition comprising C-peptide together with at least one pharmaceutically acceptable carrier or excipient. The composition does not include the presence of release rate-controlling agents.

Thus, the subject-matter of present claim 2 cannot be considered novel in view of D5 since the **product itself** is identical. The intended use (for administration as a once daily dose, for the treatment of diabetes or microvascular complications of diabetes) of the product does not establish novelty to the product *per se*.

2.3. Thus, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 2 and the hereto dependent claims 4-9 is not new in the sense of Article 33(2) PCT.

2.4. Document D1 teaches a pharmaceutical **delayed-release** formulation containing human proinsulin C-peptide and its use for treating diabetes or complications of diabetes.

Document D3 relates to a composition comprising C-peptide of proinsulin and polyunsaturated fatty acids.
The daily dose of these compounds may not exclude the administration of long acting preparations or depot preparation once (or more times) in a day. However, this disclosure is in relation to the treatment of cancer and **not diabetes**.

D4 refers to **depot forms** of proinsulin C-peptide, N-0923 or levodopa.

Thus, the subject-matter of claims 1 and 3 is new in the sense of Article 33(2) PCT.

3. Inventive step

3.1. Claim 2 and the hereto dependent claims 4-9:

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 2 and 4-9 does not involve an inventive step in the sense of Article 33(3) PCT (see lack of novelty under point 2.3.).

3.2. Claims 1 and 3:

Document D4, which is considered to represent the most relevant state of the art, discloses depot formulations comprising proinsulin C-peptide as a once daily dose for the treatment of microvascular diabetic complications.

The subject-matter of claim 1 (and 3) of the present application differs from document D4 in that **no release rate-controlling** agents are present.

In the light of the present claims, description and having regard to the prior art, the problem to be solved by the above claims can be formulated as 'provision of an improved method for treating diabetes and/or microvascular diabetic complications'.

The solution proposed in claim 1 (and 3) of the present application can be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

C-peptide is known to have a relatively short half-time. Due to the short half-life of C-peptide, prior art disclosures several days doses, a continuously administered dose or delayed release formulations.

However, the inventors of the present application have surprisingly found that C-peptide given in a once daily dose can be used to treat diabetes (even in the absence of any release rate-controlling agents or continuous administration).

The prior art does not provide any indication that would prompt the skilled person to

use a C-peptide formulation (without any release rate-controlling agents or continuous administration) as a medicament for once daily administration for the treatment of diabetes, thus rendering the invention of claims 1 and 3 non-obvious.

4. Method of treatment

For the assessment of the present claim 3 (and the hereto dependent claims 4-9) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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Claims

1. Use of C-peptide in the manufacture of a medicament for administration to a patient as a once daily dose for the treatment of diabetes and/or microvascular diabetic complications, wherein said once daily dose does not include a continuous administration or the presence of release rate-controlling agents.

2. A pharmaceutical composition comprising C-peptide together with at least one pharmaceutically acceptable carrier or excipient for administration to a patient as a once daily dose, wherein said once daily dose does not include a continuous administration or the presence of release rate-controlling agents for the treatment of diabetes and/or microvascular diabetic complications.

3. Method of treating diabetes and/or microvascular diabetic complications comprising administering C-peptide or a pharmaceutical composition comprising C-peptide to a patient in a once daily dose, wherein said once daily dose does not include a continuous administration or the presence of release rate-controlling agents.

4. Use, pharmaceutical composition or method according to any one of claims 1 to 3 wherein the C-peptide is human C-peptide.

5. Use, pharmaceutical composition or method according to any one of claims 1 to 4 wherein said C-peptide is the fragment EGSLQ (SEQ ID NO. 2).

6. Use, pharmaceutical composition or method according to any one of claims 1 to 5 wherein the patient is a human.

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7. Use, pharmaceutical composition or method according to any one of claims 1 to 6 wherein the medicament contains 100 to 1800 nmol of C-peptide.

8. Use, pharmaceutical composition or method according to any one of claims 1 to 7 wherein the medicament is an uncompromised aqueous solution.

9. Use, pharmaceutical composition or method according to any one of claims 1 to 8 wherein said complications are diabetic nephropathy, retinopathy or neuropathy.

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